UNITED STATES DEPARTMENT OF COMMERCE
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SERIAL NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTORNEY DOCKET NO.
08/535,556	09/28/95	FALO L	125350

18N2/0806

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EXAMINER	
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ART UNIT	PAPER NUMBER
1804	

DATE MAILED: 08/06/96

Please find below a communication from the EXAMINER in charge of this application.

Commissioner of Patents

Office Action Summary	Application No. 08/535,556	Applicant(s) Falo et al.
	Examiner Jill Schmuck	Group Art Unit 1804

☒ Responsive to communication(s) filed on *Sep 28, 1995* .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-67* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-67* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

Specification

1. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to adequately teach how to use the invention; i.e., failing to provide an enabling disclosure.

The claimed invention is broadly directed to an in vivo or ex vivo method of genetic immunization by delivery of a particulate polynucleotide which expresses an antigenic protein or antigenic protein fragment to a target cell of a mammalian host via the MHC class I pathway. In view of the unpredictable and complex nature of the subject matter, however, the claimed invention is unlikely to be accepted in the absence of clear and convincing data.

In the field of gene therapy, particle bombardment is an effective means of gene transfer both in vitro and in vivo in mouse models. However, according to Schofield and Caskey (British Medical Bulletin, 1995), "The requirement for a surgical procedure has also been cited as a major limitation in transferring this technology to human subjects." Schofield and Caskey also note the "wide variations in the efficiency of overall gene expression" associated with particle bombardment.

They further disclose that "Analysis have shown that once inside the cell the foreign DNA does not integrate into the host cell genome, and exists as a relatively unstable episome." (page 59, columns 1 and 2). In fact, Schofield and Caskey disclose that "At present no preferred technique has emerged as a clear favourite for non-viral delivery. Further refinement of the technology with particular emphasis on achieving long-term gene expression is required before initiating clinical trials on non-viral gene delivery." (page 57, introduction).

Furthermore, as evidenced by Marshall (Science, 1995), the field of gene therapy is unpredictable and undeveloped. Marshall discloses that there are over 100 gene therapy clinical trials approved, directed toward cancer, AIDS, cystic fibrosis, and other diseases, but that "so far, there has been no unambiguous evidence that genetic treatment has produced therapeutic benefits" (page 1050, first column). Marshall discloses the observation of NIH Director Harold Varmus, that "despite the growing support for gene therapy, [the field] remains at an early stage of development. While there are several reports of convincing gene transfer and expression, there is little or no evidence of therapeutic benefit in patients-or even in animal models." (page 1050, second column). In addition, Coghlan (Focus, 1995) and Brown (The Washington Post, 1995) teach that methods wherein nucleic acid expression vectors are administered to living subjects to introduce therapeutic proteins have not yet

been shown to operate successfully to provide therapeutic benefit to patients, and that much more experimentation is needed before gene therapy develops into a useful, operable means for treating disease. Thus, based on the disclosures of Schofield and Caskey, Marshall, Coghlan, and Brown, emphasizing the unpredictability of gene therapy, one of skill in the art would not accept a method of gene therapy for the purpose of genetic immunization.

In addition, according to Bignon et al. (European Journal of Dermatology, 1996), in early 1995, several gene therapy protocols associated with melanoma have been launched. These protocols are designed to evaluate toxicity and dosage, rather than therapeutic efficiency (page 161, column 1). They disclose that "The initial first trials of cytokine gene transduction in immune cells were disappointing, mainly because of the difficulty of efficiently transducing cytokines in lymphocytes instead of tumoral cells (hence, cytokine production was often too low)." It follows that "No assessment, in terms of therapeutic efficiency, has been published". Bignon et al. also disclose that "Cell types present in the infiltrate vary according to the therapeutic gene used. For example, it appears the CD8+ T cells are required for IL-2 or TNF activity." They also disclose that "Allogenic cells are easier to handle than autologous cells for therapeutic use, but preliminary tests showed that antibodies produced are directed against alloantigens in 99% of cases, and never against melanoma specific antigens." (page 161, column 2, 1st full and 2nd

paragraphs). All of the disclosed protocols represent a model to study for gene immunotherapy trials, however, initial results, in terms of therapeutic efficiency, appears to be lacking.

Furthermore, Bignon et al. disclose there is a discrepancy in distinguishing between tumor specific antigens and tumor associated antigens. "So, the lack of immunoreactivity in spontanteous cancers would be due, more to a lack of knowledge of the way to become immunized against these antigens rather than to a defect of target molecules for the immune system. Most of the immune responses against tumors detected in humans are of low efficiency in vivo, whereas, in vitro, the lymphocyte cytotoxicity can be very strong." (page 161, column 2, 3rd paragraph). Unfortunately, in many of the disclosed strategies, "even if efficiency was observed in mice, the therapeutic approach is limited by the need to treat all tumoral cells to obtain tumoral eradication." (paragraph bridging pages 161-162). Likewise, Cournoyer and Caskey (Annu. Rev. Immunol., 1993) note that "results in animals" from trials concerning gene transfer into tumor cells "were variable, and the applicability of these findings to human treatment remains to be established." (page 320, column 2, 1st full paragraph).

Bignon et al. disclose other difficulties associated with immunotherapy. For example, "Cytokine overproduction is not a criterion of increased efficiency: IL-2 activity is of the 'bell curve type' (higher doses having a lower action than optimal

doses) as compared to GM-CSF for which a 'plateau effect' is observed. Cytokine production usually induces a reactional production of other cytokines by the body which can potentiate the first, but can also inhibit them and would have to be controlled. The vaccine effect observed in animals depends on the number of cells reinjected to test it". "Efficiency of gene transfer is still low whatever the vector." (page 162, column 1, 4th full paragraph).

As of this date, there are still many outstanding questions associated with gene therapy for genetic immunization, only supporting the unpredictability of the field. For instance, "Will we be able to extrapolate results obtained in vitro or in vivo for animals to humans? Do we have good experimental models? Dermatological cancers, primary gene therapy targets, are multigenic and multifactorial diseases: will gene therapy take into account all genes involved in this tumor pathogeny?" (page 162, column 1, 4th full paragraph). Thus, the disclosure of Bignon et al., and Cournoyer and Caskey, indicate that there is a high degree of unpredictability associated with the methods as claimed herein.

The specification offers several working examples, of which illustrate genetic immunization by biolistic administration or subcutaneous administration of the particulate polynucleotide, pAc-Neo-OVA, in a mouse model. The working examples determined that protective immunity was antigen-specific and that CD8+

effector cells were essential. Direct subcutaneous injection and biolistic administration of the particulate polynucleotide was disclosed to produce equivalent results in the mouse model used.

Upon consideration of the working examples disclosed, many aspects of the claimed invention are clearly deficient in the specification. For example, the working examples only show support for a particulate polynucleotide comprised of the pAc-Neo-OVA. The claims read on the employment of any type of particulate polynucleotide expressing an antigenic protein or antigenic protein fragment. The melanoma B17 and OVA peptide have both been under extensive study, and therefore are well known in the art. Employment of a particulate polynucleotide in the claimed invention having different and/or unknown structural and functional properties may lead to unknown and possibly deleterious effects.

In addition, the claims read on inoculating a mammalian host, more specifically, a human host. However, the working examples show support only for a mouse model. Human clinical trials have a high degree of unpredictability as disclosed by Marshall, Coghlan, Brown, Bignon et al., and Cournoyer and Caskey. In fact, according to Hanania et al. (The American Journal of Medicine, 1995), "Unfortunately, the currently approved cancer vaccine trials are directed to patients in whom the balance between the tumor and its host is far different from that encountered in the animal models. For example, the tumor

burden present in the animal models is below 1 million cells, whereas the level of tumor in the patients under therapy with molecular cancer vaccines is often between 100 million to 10 billion tumor cells. In the animal models, the tumor vaccine is used in animals that have never been exposed to the tumor, whereas in the clinical trials of tumor vaccines in humans, the vaccines are being tested in patients in whom the tumor has been present for months or years." (page 542, 1st full paragraph). Also, according to the Report and Recommendations of the Panel to Assess the NIH in Research on Gene Therapy (Orkin and Motulsky, 1995), "tumorinfiltrating lymphocytes or other immune effector cells have also been transduced in an attempt to increase their specificity and/or reactivity against tumor cells. Although several of these strategies show promise in mouse models, none has demonstrated efficacy in humans" (page 6, paragraph 5).

Another important aspect in the deficiency of the specification is the dosage involved for a therapeutic effect. Based on the working example, it is unclear how much of the particulate polynucleotide or of the modified dendritic cells were injected into each mouse to elicit protective immunity or regression of tumor. Furthermore, it is unclear if a therapeutic effect entails regression of a tumor, some tumors, or all tumors. What dosage adjustment would be made in the case of a human host?

In evaluating applications in the field of gene therapy, a key ingredient is an adequate balance of several important

factors. In light of the quantity of experimentation necessary to use the invention, the amount of guidance and direction presented, consideration of the working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the degree of unpredictability of the art, and the breadth of the claims, the specification is not considered to adequately teach how to use the claimed invention. Thus, based on the high degree of unpredictability, and the described deficiencies in the specification, one of skill in the art would not accept the claimed method of gene therapy for genetic immunization.

Therefore, claims 1-67 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claim Rejections - 35 USC § 112

2. Claim 59 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The terms "biologically significant form" and "biologically significant levels" in regard to the expressed antigen presentation enhancing protein or proteins is vague and indefinite as to exactly what is intended to be encompassed.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

3. Claims 1-67 are rejected under 35 U.S.C. § 103 as being unpatentable over Nabel et al. taken with Eisenbraun et al. and further in view of Robinson et al.

Nabel et al. (Human Gene Therapy, 1992) disclose a method of immunotherapy of malignancy wherein genes, encoding a highly immunogenic molecule, an allogeneic class I major histocompatibility complex (MHC) glycoprotein, H-2K, are delivered via injection into transplantable mouse tumors. Nabel et al. disclose that it can be used alone or in combination with other genes, including cytokines, to cause tumor regression (page 400, column 2, 3rd paragraph). Nabel et al. also disclose that allogeneic class I MHC genes have been introduced into tumor

cells by transfection and subsequent selection in vitro (page 402, column 1, 2nd full paragraph).

Nabel et al. differ from the claimed invention in that the delivery of the gene encoding the antigenic protein is via DNA/liposome transfection; rather than by particle bombardment. However, at the time the claimed invention was made, Eisenbraun et al. (DNA Cell Biol., 1993) disclosed particle bombardment-mediated gene delivery (page 792, paragraph bridging columns 1 and 2) and the applications of this technique to genetic immunization were suggested. Specifically, "We favor the utilization of particle bombardment-mediated gene delivery in the further development of genetic immunization technologies because of the ability to acieve the direct, intracellular delivery of relatively small amounts of antigen-encoding expression vectors into an immunologically active tissue such as the skin." (paragraph bridging pages 791-792).

Furthermore, Robinson et al. (Vaccine, 1993) disclosed the first demonstration of protective immunity arising as a result of genetic immunization. Specifically, they reported the induction of protective immunity in chickens against lethal influenza infection following direct parental inoculation with an influenza virus hemagglutinin expression construct, thereby illustrating viral protective immunity.

Accordingly, in view of the teaachings of Eisenbraun et al. and Robinson et al., it would have been obvious for one of

ordinary skill in the art, at the time the claimed invention was made, to modify the method of gene therapy for genetic immunization taught by Nabel et al. by delivering of a particulate polynucleotide which expresses an antigenic protein or antigenic protein fragment to a target cell of a mammalian host via the MHC class I pathway for the expected effect of tumoral or viral protective immunity. Thus, the claimed invention as a whole was clearly prima facie obvious in the absence of evidence to the contrary.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jill Schmuck whose telephone number is (703)305-2147.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasemine C. Chambers, can be reached on (703)308-2035. The fax number for this Group is (703)308-4312.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703)308-0196.

Jasemine C. Chambers

JASEMINE C. CHAMBERS
PRIMARY EXAMINER
GROUP 1800

Jill Schmuck

July 31, 1996